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CASE REPORT

First report of successful transplantation of a pediatric donor liver graft after hypothermic machine perfusion

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Abstract

One of the main limiting factors in pediatric liver transplantation is donor availability. For adults, DCD liver grafts are increasingly used to expand the donor pool. To improve outcome after DCD liver transplantation, ex situ machine perfusion is used as an alternative organ preservation strategy, with the supplemental value of providing oxygen to the graft during preservation. We here report the first successful transplantation of a pediatric DCD liver graft after hypothermic oxygenated machine perfusion. The full-size liver graft was derived from a 13-year-old, female DCD donor and was end-ischemic pretreated with dual hypothermic oxygenated machine perfusion. Arterial and portal pressures were set at 18 and 4 mm Hg, slightly lower than protocolized settings for adult livers. During 2 hours of machine perfusion, portal and arterial flows increased from 100 to 210 mL/min and 30 to 63 mL/min, respectively. The pretreated liver graft was implanted in a 16-year-old girl with progressive familial intrahepatic cholestasis type 2. Postoperative AST, ALT, and prothrombin time normalized within a week. The recipient quickly recovered and was discharged from the hospital after 18 days. One year after transplantation, she is in excellent condition with a completely normal liver function and histology. This case is the first report of successful transplantation of a pediatric DCD liver graft after hypothermic oxygenated machine perfusion and illustrates the potential role of ex situ machine perfusion in expanding the donor pool and improving outcome after pediatric liver transplantation.

KEYWORDS

donation after circulatory death, hypothermic oxygenated machine perfusion, pediatric liver transplantation

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCD, donation after circulatory death; GGT, gamma-glutamyl transferase; HMP, hypothermic machine perfusion; UW, University of Wisconsin.

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1 | INTRODUCTION

Orthotopic liver transplantation is the only effective therapy in patients with end-stage liver disease. Still, donor availability is the main limiting factor in liver transplantation, especially in pediatric patients, who need a perfect size-appropriate graft.¹ To expand the number of suitable liver grafts for pediatric recipients, several technical variants are practiced, including splitting of deceased adult donor liver grafts and the use of living donors. Despite this, waiting list mortality rate is up to 20%.² Moreover, during the period on the waiting list children are at great risk of growth and developmental retardation.

For adults, DCD liver grafts are increasingly used to expand the donor pool. Good results with transplantation of DCD liver grafts are reported, but a major concern remains the high rate of biliary complications. For children, the use of DCD grafts is still controversial and the available data are limited to small series.^{3,4}

To improve outcome of DCD liver transplantation, ex situ HMP is increasingly used as an alternative strategy for organ preservation, with the supplemental value of providing oxygen to the graft during preservation.⁵ The initial experience in adults has demonstrated that end-ischemic HMP provides better preservation of DCD liver grafts. HMP ameliorates ischemia-reperfusion injury in DCD liver grafts by restoring mitochondrial function before implantation, and it offers better preservation of the bile ducts and their vasculature.^{6,7} This is an important step forward in reducing biliary complications after DCD liver transplantation.

So far, machine perfusion has only been reported in adult to adult liver transplantation. We here report the first successful transplantation of a pediatric DCD liver graft after oxygenated HMP.

1.1 | Case Presentation

The liver graft was derived from a 13-year-old, female DCD donor (65 kg, 167 cm), who was resuscitated after an out of hospital cardiac arrest. She was admitted to the intensive care unit for 7 days. Last serum ALT before procurement was 65 U/L, and last serum sodium was 162 mmol/L. The agonal phase between withdrawal from life support until circulatory arrest was 19 minutes. After a mandatory 5 minutes "no touch period," rapid cannulation of the aorta was performed and the liver was in situ perfused with ice-cold Belzer UW cold storage solution (supplemented with heparin). The total period from withdrawal of life support to in situ cold perfusion endured 34 minutes. The bile ducts were gently flushed in a retrograde fashion with UW preservation solution. Subsequently, the liver was packed static cold storage and transported to our center.

In our center, the liver graft was inspected and appeared to be of good quality. Liver weight was 1509 g. Because the liver was derived from a DCD donor and to minimize further ischemic injury as much as possible, it was decided to prepare the liver graft for oxygenated HMP during recipient hepatectomy. A conventional back table procedure of the graft was performed after which the portal vein and suprarenal aorta were cannulated for machine perfusion.

Subsequently, the liver underwent pressure-controlled dual hypothermic oxygenated machine perfusion using the Liver Assist (Organ Assist, Groningen, The Netherlands). The perfusion fluid consisted of 4000 mL Belzer UW machine perfusion solution, supplemented with 3420 mg glutathione. Perfusion fluid was oxygenated with 1 L/min 100% O₂ to obtain a PaO₂ of >70 mm Hg, and temperature was kept at 10°C, according to our HMP protocol.⁶ Arterial and portal pressures were set at 18 and 4 mm Hg, respectively, which is slightly lower than our protocolized settings for adult livers (25 and 5 mm Hg, respectively). During HMP, portal flow increased adequately from 100 to 210 mL/min and arterial flow from 30 to 63 mL/min, whereas pressure and temperature remained stable (Figure 1). Perfusate glucose level increased in the first 30 minutes of HMP from 8.8 to 12.5 mmol/L and remained stable thereafter. The perfusate lactate level decreased from 2.4 to 1.7 mmol/L. After 2 hours of HMP, the liver was disconnected from the perfusion machine and transplanted.

The selected recipient was a 16-year-old girl (42 kg, 156 cm), who was diagnosed in the neonatal phase with progressive familial intrahepatic cholestasis type 2. To prevent progressive damage of the hepatocytes by retention and accumulation of bile salts, a partial external biliary diversion procedure was performed when she was 4 years old.⁸ Despite this, at the age of 14 years she was listed for liver transplantation because of deterioration of cholestasis with icterus and itching, and bile stoma bleedings. The recipient and her parents gave consent to receive a HMP-preserved DCD liver.

The HMP-pretreated full-size liver graft was implanted using the piggyback technique with end-to-end portal and arterial anastomoses. Perioperative blood loss was 1800 mL, and the recipient received one red blood cell transfusion (280 mL) intraoperatively. Total cold preservation time of the donor liver graft was 512 minutes, consisting of 384 minutes of cold ischemic storage and 128 minutes of oxygenated HMP. Subsequent warm ischemia time was 33 minutes. Immediately

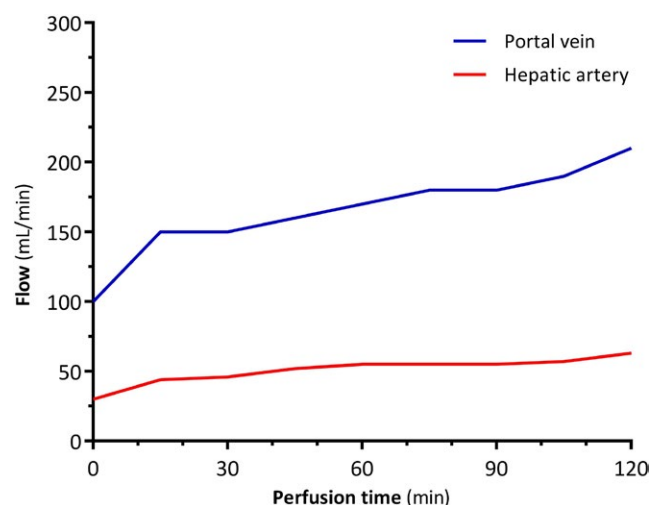
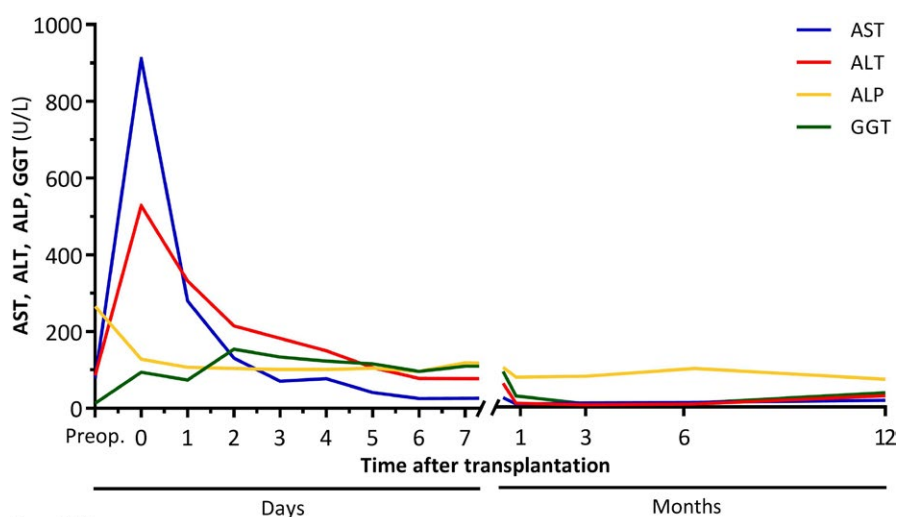


FIGURE 1 Portal and arterial flow rates during two hours of dual hypothermic oxygenated machine perfusion of a 13-year-old DCD liver graft. The perfusion machine was pressure-controlled with portal pressure set at 4 mm Hg and arterial pressure set at 18 mm Hg. DCD, donation after circulatory death

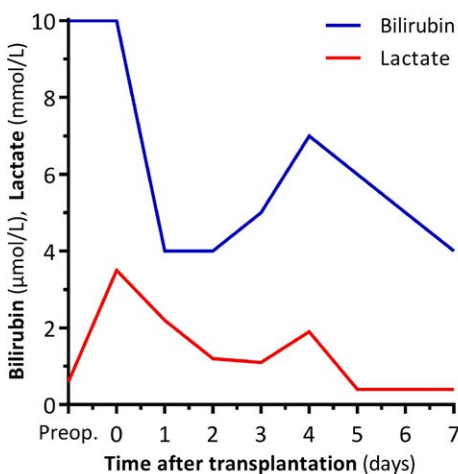
after transplantation, the recipient was extubated and admitted to the pediatric intensive care unit where vasopressive support could be reduced to zero and intravenous heparin was administered as is routine practice after pediatric transplantation in our center. Postoperative AST, ALT, and prothrombin time rapidly decreased and normalized within a week (Figure 2A). ALP and GGT normalized within a month and remained stable afterward. Immediate postoperative lactate was 3.5 mmol/L and levels steadily decreased thereafter, with a small second peak on postoperative day four when an intra-abdominal bleeding was diagnosed, which required surgical intervention (Figure 2B). Surgical inspection showed diffuse oozing with a potential bleeding focus at the inferior vena cava, which was clipped, and additionally, a hematoma was evacuated. After this, the recipient had a quick and further uneventful recovery until she was discharged from the hospital on postoperative day 18. One year later, the recipient is in excellent condition with a completely normal liver function with a serum ALT of 16 U/L, bilirubin of 7 $\mu\text{mol/L}$, and a normal liver histology on routine liver biopsy. There were no clinical or histological signs of biliary complications, and additional imaging was not performed.

2 | DISCUSSION

This case report describes the first successful transplantation of a pediatric DCD liver graft after ex situ oxygenated HMP. There are only a few descriptions of pediatric liver transplantations with grafts from DCD donors in the current literature.^{3,4,9} Hong et al reported a matched case-control study of 7 DCD liver transplantations in pediatric patients with excellent long-term outcomes.³ A biliary anastomotic stricture occurred in only one of the recipients, and the incidence of biliary complications was not different between DCD and donation after brain death liver transplantations. Also Gozinni et al have suggested that liver grafts from young DCD donors with short ischemia times can be safely used in pediatric transplantation.⁹ Moreover, van Rijn et al demonstrated that transplantation of pediatric DCD liver grafts results in good long-term outcomes, when the donor warm ischemia time is kept under 30 minutes.⁴ Patient and graft survival rates were comparable to those of pediatric donation after brain death liver grafts. Moreover, the incidence of non-anastomotic biliary strictures



Panel(A)



Panel(B)

FIGURE 2 Panel A: Serum AST, ALT, ALP, and GGT levels in a 16-year-old recipient after successful transplantation of a hypothermic oxygenated machine perfused pediatric DCD liver graft. Panel B: Serum bilirubin and lactate in a 16-year-old recipient after successful transplantation of a hypothermic oxygenated machine perfused pediatric DCD liver graft. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; DCD, donation after circulatory death

after transplantation of pediatric DCD livers was remarkably low. These studies support the use of pediatric DCD liver grafts for transplantation.

A major drawback of DCD liver grafts is the devastating effect of warm with subsequent cold ischemia, leading to depletion of intracellular energy sources, such as adenosine 5'-triphosphate, combined with other metabolic disturbances. This results into cellular injury and dysfunction due to reperfusion injury during transplantation.^{10,11} Ischemia-reperfusion injury is a major cause of primary non-function, early allograft dysfunction, and biliary complications after transplantation.¹²

In adult liver transplantation, it has been demonstrated that a short period (1-2 hours) of oxygenated HMP after traditional static cold storage restores the hepatic energy status in liver grafts, reduces ischemia-reperfusion injury and improves early graft survival.^{5,6,13} Based on these experiences, we decided to apply end-ischemic HMP to the pediatric DCD liver graft offered to our recipient. Compared to adult liver grafts, pediatric livers are smaller and potentially more susceptible to intravascular pressure-induced damage. This is important because one of the potential risks of HMP is endothelial injury due to shear stress. Shear stress occurs in case of high perfusion pressures, especially at low temperatures when endothelial cell membranes are susceptible to injury.¹⁴ Perfusion-induced endothelial cell injury can be prevented by using low perfusion pressures and a pressure-controlled perfusion system.^{13,15} Therefore, we used a pressure-controlled machine perfusion device with arterial and portal perfusion pressures lower than values generally used for adult liver grafts.¹⁶

In the reported case, we demonstrated HMP of a 13-year-old DCD liver graft, which was relatively large. To determine optimal portal and arterial pressures for HMP in pediatric liver grafts, more experiences and research are required. In our opinion, perfusion pressures in pediatric liver grafts should be lowered based on donor age, to adjust for the lower physiological pressure in the liver graft. For HMP in adult liver grafts, protocolized portal and arterial perfusion pressures are set at 3-5 and 25 mm Hg, respectively.^{6,13} Normally, an adult liver graft is used to a physiological mean arterial blood pressure of 90 mm Hg in the donor, whereas pediatric liver grafts are used to lower systemic blood pressures. Perhaps we should lower perfusion pressures for pediatric liver grafts based on donor mean arterial blood pressures according to donor age. For example, a 5-year-old pediatric liver graft is used to a mean arterial blood pressure of 65 mm Hg, which is about 30% lower when compared to 90 mm Hg in adults. Therefore, it seems reasonable to reduce the portal and arterial pressure with 30%, leading to a portal and arterial perfusion pressure of 3-4 and 18 mm Hg during HMP, respectively.

In the coming years, further advances in organ preservation, such as machine perfusion, may provide a solution to the problem of donor organ scarcity for pediatric patients. Machine perfusion of DCD donor grafts might reduce part of the risks of DCD liver transplantation. With this case, we demonstrated that HMP of a pediatric liver graft is feasible and can be performed safely with adjusted perfusion pressures.

Apart from providing a better preservation method, machine perfusion can also facilitate pediatric liver transplantation by enabling a split procedure of a liver graft under continuous oxygenated perfusion. The concept of splitting a liver graft during machine perfusion was recently shown by Stephenson et al.¹⁷ These investigators successfully performed a split procedure of an adult liver graft resulting in a segment 2/3 and an extended right lobe graft. In addition, with the upcoming technique of normothermic machine perfusion, which enables ex situ functional assessment of the liver graft prior to implantation, it might be useful to estimate the suitability of a suboptimal liver graft for a pediatric recipient.¹⁸ Altogether, this may increase the number of liver grafts that are suitable for pediatric liver transplantation.

In conclusion, we present the first successful transplantation of a pediatric DCD liver graft after ex situ hypothermic oxygenated machine perfusion. This case illustrates the potential role of ex situ machine perfusion technology in expanding the donor pool and improving outcome after pediatric liver transplantation.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

Mrs Werner: Collected and analyzed the data, drafted the initial manuscript, and critically reviewed and edited the manuscript; Mr van Leeuwen and Ms de Jong: Collected the data and critically reviewed and edited the manuscript; Ms de Vries: Designed the study and critically reviewed and edited the manuscript; Dr Bodewes, Mr Fujiyoshi, Dr Luhker, Dr Scheenstra, and Mr de Kleine: Supervised data interpretation and critically reviewed and edited the manuscript; and Dr Porte: Designed the study, supervised data analysis and interpretation, and critically reviewed and edited the manuscript. All authors approved the final manuscript as submitted.

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